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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,987	CHAMBERLAIN ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on th cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 21 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment to pg 1, line 3, has been entered. The amendment to the description of Fig. 1 has been entered.

Applicant's arguments filed 8-11-03 have been fully considered but they are not persuasive. Claims 1-8, 21 and 22 remain pending in the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Objections

The phrase "the DNA vector" in claim 1 (both occurrences) should be –the recombinant vector--.

Claim Rejections - 35 USC ' 112

1. Claims 1-8, 21 and 22 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing a CTL response in a mammal comprising administering a vaccinia viral vector encoding an antigen operably linked to a promoter followed by administering a fowlpox vector encoding said antigen operably linked to a promoter such that a CTL response against said antigen occurs as compared to vaccinia followed by vaccinia, fowlpox followed by fowlpox or fowlpox followed by vaccinia, does not reasonably provide enablement for inducing a therapeutic or prophylactic immune response against an antigen using the

claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for reasons of record.

While the claims do not require inducing a therapeutic or prophylactic immune response against an antigen, inducing a therapeutic or prophylactic immune response against an antigen is the only disclosed use for inducing an immune response in a mammal. The specification teaches inducing an immune response against β-gal to find methods of vaccination that generate a CTL or antibody response that is therapeutic or prophylactic (pg 4, lines 2-13) and inducing an immune response against cancer (original claim 9). Therefore, the claims are being considered under enablement for their only disclosed use, i.e. inducing a therapeutic or prophylactic immune response against an antigen.

The specification does not enabled one of skill to use the method claimed to induce a therapeutic or prophylactic immune response against an antigen.

It was known in the art at the time of filing that the combination of vector, promoter, antigen, target tissue, level of expression and route of administration required to target the desired tissue and obtain a therapeutic or prophylactic effect using gene therapy was unpredictable (Miller, 1995, FASEB J., Vol. 9, pages 190-199; pg 198, col. 1; Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69; pg 53, 1st ¶, pg 65, 1st ¶ under Conclusion; Verma, Sept. 1997, Nature, Vol. 389, pages 239-242; see entire

article, pg 240, sentence bridging col. 2-3; Crystal, 1995, Science, Vol. 270, pg 404-410; pg 409, all of record).

It was known in the art that a CTL response against β-gal could be induced upon administering wild-type vaccinia followed by a fowlpox vector encoding β-gal (Wang, 1995, J. Immunol., Vol. 154, pg 4685-4692), or by administering wild-type fowlpox followed by vaccinia virus encoding β-gal (pg 4689, col. 2, last sentence). However, the art did not teach the immune response was therapeutic or prophylactic.

The specification demonstrates administering a vaccinia, fowlpox or plasmid vector encoding β-gal followed by a different boosting vector encoding β-gal and obtaining a CTL response against β-gal as compared to vaccinia followed by vaccinia or fowlpox followed by fowlpox (pg 25, Ex. 2). The specification discusses various viral vectors (pg 9-10) and various antigens (pg 11-13) to treat a variety of diseases including cancer (pg 11, lines 11-35). Example 1 teaches increasing survival of mice having β-gal-expressing tumors using vaccinia followed by fowlpox or fowlpox followed by vaccinia, each of which encode β-gal (page 21; Fig.1) and contemplates administering vectors encoding tumor associated antigens (TAA) against melanoma (example 5). The specification did not teach inducing a therapeutic or prophylactic immune response against an antigen.

The specification does not provide adequate guidance to induce a therapeutic or prophylactic immune response against an antigen because the specification does not

correlate β-gal with any other antigen or correlate the immune response obtained using vectors encoding β-gal with the immune response obtained using vectors encoding other antigens such that a therapeutic or prophylactic immune response could be obtained. β-gal tumors do not correlate to tumors having tumor-associated antigens (TAA). β-gal does not correlate to TAA because it is a foreign protein while TAA are self-proteins, because β-gal and TAA known in the art do not have the same epitopes recognized by the immune system, β-gal and TAA have different MHC restriction. The ability of β-gal (a foreign protein) and TAA (a "self" protein) differ. Specifically, the specification does not provide any guidance to treat cancer using MART-1, gp100, TRP-1 or TRP-2 because the specification does not correlate the epitope of β-gal causing an immune response with the epitope of any other antigen that may be therapeutic or prophylactic. The specification does not teach the β-gal epitope recognized by the immune system has the same amino acid sequence or structure as epitopes of MART-1, gp100, TRP-1 or TRP-2 that are recognized by the immune system. The specification does not teach MART-1, gp100, TRP-1 and TRP-2 are H-2L^d –restricted like β-gal. The specification does not teach that MART-1, gp100, TRP-1 or TRP-2 induce an equivalent immune response as β-gal.

Thus, the specification does not provide adequate guidance for one of skill to administer a vector to a mammal to obtain a therapeutic or prophylactic immune response against an antigen by teaching the level of expression of antigen required to

induce the desired immune response, how to target antigen expression to the desired tissue such that the desired immune response is obtained, or by correlating β-gal to tumor antigens such as MART-1, gp100, TRP-1 or TRP-2. Given the state of the art at the time of filing taken with the teachings in the specification, it would require one of skill undue experimentation to determine the dosage, route of administration, vector, promoter, antigens, target tissue or level of antigen expression required to obtain a therapeutic or prophylactic immune response using the claimed invention.

Applicants' discussion regarding how to make the vectors used in the method is moot. The rejection is based on how to use the method steps to induce a therapeutic or prophylactic immune response, not how to make the vectors.

Applicants argue Wang supports using β-gal as a model system to teach how to use the present invention. Applicants' argument is not persuasive because β-gal does not correlate to tumor antigens for reasons cited above and because Wang did not teach inducing a therapeutic or prophylactic immune response.

Applicants' argument regarding Neely is moot because Neely was not available at the time of filing. In addition, Neely does not teach one prostate tumor antigen that correlates to β-gal.

Applicants argue the claims do not encompass gene therapy because the specification does not recite the phrase "gene therapy." Applicants' argument is not persuasive. The examiner has established that the state of the art was that obtaining a

therapeutic or prophylactic effect using DNA encoding protein, i.e. gene therapy, was unpredictable. Therefore, inducing an immune response using vectors encoding an antigen for the purpose of therapy or prophylaxis, also well within what was well known in the art as "gene therapy," was unpredictable. Applicants argue "sustained expression of exogenous DNA" is not required for the instant invention. Applicants' argument is not persuasive because the claims require antigen expression of an amount, in an appropriate tissue and for a time adequate to induce an immune response.

Applicants' arguments regarding Dudley are not persuasive. Dudley was not available at the time of filing, does not correlate β-gal to MART-1 and does not teach obtaining a therapeutic or prophylactic effect using the claimed invention.

2. Claims 1-8 remain rejected and claims 21 and 22 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 remains indefinite because it does not clearly set forth that the inserts of the first and second vectors encode the same antigen "to which an immune response is to be induced". The phrase "wherein at least one antigen encoded by the insert of the first recombinant vector is encoded by the insert of the second recombinant vector" does not refer to "the at least one antigen to which an immune response is to be induced" in the first or second vector. Thus, it cannot be determined whether the inserts

of the first and second vectors encode the same antigen "to which an immune response is to be induced. The phrase –i) inoculating the mammal with a first recombinant vector comprising a nucleic acid insert encoding an antigen; and ii) inoculating the mammal with a second recombinant vector comprising a nucleic acid insert encoding said antigen, wherein the first recombinant vector is different from the second recombinant vector—would overcome this rejection. The phrase "an antigen" is open language and has the same scope as "at least one antigen".

Claim 5 as newly amended is indefinite because it is unclear if "the insert of the recombinant vector" refers to the insert of the first or second recombinant vector.

Claims 21 and 22 as newly amended are indefinite because it is unclear if "said at least one antigen..." refers to "said at least one antigen" encoded by the first recombinant vector, the second recombinant vector or at least one antigen encoded by both the first and second recombinant vector.

Claim Rejections - 35 USC ' 103

3. Claims 1-3 and 5-7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (May 1, 1995, J. Immunol., Vol. 154 (9) 4685-92).

Wang taught administering a wild-type vaccinia virus (VV) to mice followed by administering a fowlpox virus (FPV) encoding β-gal which caused an increase in CTL response in splenocytes as compared to administering wild-type vaccinia followed by

vaccinia encoding β-gal (page 4689, col. 2, Fig. 6, 1st full para.). The increased CTL response is "an immune response" against the "at least one antigen" as claimed. Wang did not teach administering VV-β-gal followed by administering FPV-β-gal. However, Wang taught a vaccinia VV-β-gal. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer VV-β-gal followed by FPV-β-gal as taught by Wang. One of ordinary skill in the art at the time the invention was made would have been motivated to replace wild-type VV with VV-β-gal to introduce the DNA encoding β-gal sooner thereby inducing the immune response sooner.

Similarly, Wang taught administering a wild-type FPV followed by VV-β-gal, which also caused an immune response (page 4689, col. 2, 1st para.). Wang did not teach administering FPV-β-gal followed by VV-β-gal. However, Wang taught administering FPV-β-gal caused an immune response. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer FPV-β-gal followed by VV-β-gal. One of ordinary skill in the art at the time the invention was made to replace wild-type FPV with FPV-β-gal to introduce the DNA encoding β-gal sooner and induce the immune response sooner. Claim 5 is included because VV and FPV encode viral proteins that are recognized as foreign and induce an immune response.

Applicants argue the examiner has applied the standard for obviousness incorrectly. Applicants argue Wang does not suggest modifying the method described in Wang. Applicants argue Wang does not provide a reasonable expectation of successfully inducing an immune response. Applicants' arguments are not persuasive.

Wang taught administering a wild-type FPV followed by VV-β-gal. Therefore, Wang taught administering two different vectors. Wang taught administering FPV-β-gal followed by FPV-β-gal (Fig. 5C). Therefore, Wang taught administering FPV-β-gal first followed by a second vector encoding β-gal, i.e. pre-immunization with FPV-β-gal. While Wang did not teach administering two different vectors both encoding β-gal, when taken together, Wang taught all the limitations claimed.

Wang need not explicitly state the wild-type virus in Fig. 6 should be replaced with virus encoding β-gal. Motivation may also be determined based on the knowledge of one of ordinary skill in the art at the time the invention was made. In this case, motivation to replace wild-type FPV with FPV-β-gal comes from the knowledge of one of ordinary skill in the art at the time the invention was made to introduce the DNA encoding β-gal sooner thereby inducing the immune response sooner. Replacing FPV with FPV-β-gal was well within the knowledge of one of ordinary skill in the art at the time of filing because those of ordinary skill in the art at the time of filing readily exchanged vectors in protocols. Inducing an immune response sooner was also well

within the knowledge of one of ordinary skill in the art at the time of filing. Evidence of exchanging vectors is seen in Wang who taught numerous combinations of vectors.

Wang provides a reasonable expectation of success in inducing an immune response using FPV-β-gal followed by VV-β-gal because FPV-β-gal induced an immune response and FPV-wild-type followed by VV-β-gal induced an immune response.

4. Claims 1-3, 5-7, 21 and 22 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (May 1, 1995, J. Immunol., Vol. 154 (9) 4685-92).

Wang taught administering VV-β-gal to mice followed by FPV-β-gal or vice versa, which caused an immune response (see 103 rejection above). Wang did not expressly teach replacing β-gal with MART-1 or gp100. However, Wang suggested replacing β-gal with MART-1 and gp100 and taught making FPV-MART-1 and FPV-gp100 (pg 4690, col. 2, last 2 ¶). Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Wang wherein the β-gal gene is replaced with MART-1 or gp100 as suggested by Wang. One of ordinary skill in the art at the time the invention was made would have been motivated to replace β-gal with MART-1 or gp100 to determine if self proteins such as MART-1 or gp100 induced the same immune response as β-gal and to determine if MART-1 or gp100 enhanced the precursor frequency of T-cells that recognize MART-1 or gp100 prior to *ex vivo* expansion (pg 4690, col. 2, ¶ 2, line 4).

Applicants have not argued this rejection.

5. Claim 1-8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wang (J. Immunol., (1995 May 1) 154 (9) 4685-92) in view of Zhai (Jan. 15, 1996, J. Immunol., Vol. 156, No. 2, pages 700-710).

Wang taught administering VV-β-gal to mice followed by FPV-β-gal, which caused an increase in CTL response in splenocytes as compared to administering two doses of vaccinia virus encoding β-gal. Wang did not teach replacing the vaccinia virus or fowlpox virus with an adenovirus. However, Zhai taught administering an adenoviral vector encoding β-gal to mice and obtaining an immune response.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the method of Wang wherein the vaccinia virus or fowlpox virus was replaced with the adenoviral vector taught by Zhai. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the vaccinia virus (the first vector) with the adenoviral vector to increase the CTL response against antigen as compared to administering adenoviral vector followed by readministration of adenoviral vector. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the fowlpox virus (the second vector) with the adenoviral vector to determine if fowlpox was the only virus that

could be used to obtain a CTL response against antigen after administering vaccinia virus.

Applicants mention the deficiencies of Wang and Zhai but do not provide any specific arguments regarding why the combined teachings of Wang and Zhai do not teach all the limitations of the claims or why motivation is lacking (pg 9 of response). Applicants' argument is not persuasive. The combined teachings of Wang and Zhai taught all the limitations of claim and one of ordinary skill in the art would have been motivated to combine the teachings of Wang and Zhai.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

No claim is allowed.

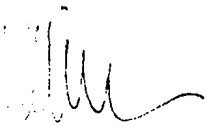
Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson



MICHAEL WILSON
PRIMARY EXAMINER